Title
Resting-state functional connections of trait extraversion and neuroticism in autistic individuals

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Resting-state functional connections of trait extraversion and neuroticism in autistic individuals

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Education

by

An Chuen Cho

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ABSTRACT OF THE DISSERTATION

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by

An Chuen Cho

Doctor of Philosophy in Education

University of California, Los Angeles, 2021

Professor Jeffrey J. Wood, Chair

Introduction: Personality psychologists have made notable contributions to various clinical fields by incorporating an *individual differences* framework that is substantiated by neurobiological evidence. Recent autism research has employed this approach to explain the heterogeneity within the disorder; however, the neurobiological bases of personality in the ASD population remains unclear. In order to fully integrate this framework, it is necessary to investigate the neurological correlates of personality in autistic individuals and evaluate the extent it reflects findings in the normative population.

Objectives: To identify resting-state functional connections associated with Extraversion and Neuroticism in autistic participants (ASD) in contrast to neurotypical peers (TYP).

Method: The present study utilized secondary data from a longitudinal cognitive functioning study. After removing cases for excessive motion, 150 participants (ASD [n=73]: M_{age}=17.42, SD_{age}=3.00; TYP [n=77]: M_{age}=16.92, SD_{age}=3.10) had sufficient data for analyses. ROI-ROI connections associated with Extraversion or Neuroticism were identified in ASD and TYP independently, and the two groups were evaluated together to identify potential interaction effects between personality and ASD diagnosis.

Results: In the ASD group, two connections (left parietal medial cortex – left retrosplenial cortex; left parietal medial cortex – right precuneus) were positively associated and one connection (left dorsal prefrontal cortex – right midcingulate cortex) was negatively associated with Neuroticism. The latter connection also presented differential associations with Neuroticism between ASD and TYP (p-FDR=.0250; TYP r=.207, ASD r=-.435). Exploratory analyses found that, in the ASD group, these connections were also associated with secondary measures of psychopathology, a relationship that was fully mediated by Neuroticism.

Discussion: The identified connections were all related to functions of attention and memory, suggesting mechanisms linked to (over)sensitivity to negative stimuli and repetitive negative thinking. In particular, the left dorsal prefrontal cortex – right midcingulate cortex connection may be indicative of a compensatory mechanism biomarker in autistic individuals. This study serves as the first neuroimaging study in the emerging field of personality-related autism research, which aimed to tackle questions about the neural substrates of the endophenotypes of personality in the ASD population.

The dissertation of An Chuen Cho is approved.

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2021

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Autistic individuals[1] may differ in their clinical characteristics (e.g., symptomatology, comorbidity, developmental trajectory) as well as their neurobiology (Chen et al., 2019; Kim et al., 2016; Lai et al., 2019). Recent literature has highlighted this heterogeneity as a challenge to scientific progress (Hong et al., 2020; Masi et al., 2017), noting that "understanding this multi-level heterogeneity is of high clinical and translational importance" (Lombardo et al., 2019, p. 1435). To address this challenge, researchers have emphasized the need to establish a dimensional approach that could adequately capture the spectrum of complex presentations within autism spectrum disorders (ASD) (Georgiades et al., 2013).

[1] The present manuscript uses identity-first language (e.g., "autistic individuals") in efforts to recognize and validate individuals' value and worth as autistic persons. However, it should be noted that some individuals may prefer the use of person-first language (e.g., "individuals with autism") and I apologize in advance if the present identity-first language causes anyone discomfort.

The growing subfield of personality-related autism research presents a promising means of potentially disentangling the heterogeneity within ASD. This line of research is modeled after other clinical fields that have successfully adopted the *five-factor model of personality* (*FFM*) framework to better understand the variability present in other clinical disorders (e.g., attention-deficit hyperactivity disorder [Gomez & Corr, 2014], psychopathy [Patrick & Drislane, 2015]). This framework implements a dimensional approach to characterize individual differences across five personality domains (extraversion, agreeableness, conscientiousness, neuroticism, openness to experience) and may help to further explain both the phenotypic variability across individuals as well as the neurobiology and developmental outcomes that map onto those differences (Kotov et al., 2017; Lengel et al., 2016). Furthermore, personality traits have been shown to be associated with mental health treatment outcomes across various clinical disorders (e.g., agreeableness is positively

associated with therapeutic alliance), suggesting client personality may highlight potential strengths and barriers in treatment (Bucher et al., 2019).

A recent meta-analysis of ASD personality studies found that autistic individuals significantly differed from their non-clinical peers across all five FFM domains, and all five domains were independently correlated with autism symptom severity (Lodi-Smith et al., 2019). Specifically, autistic individuals had higher neuroticism and lower extraversion, agreeableness, conscientiousness, and openness to experience than non-clinical counterparts, with the largest effects in extraversion and neuroticism. One study included in the meta-analysis identified distinct personality-based subgroups that differed across several demographic and criterion variables (e.g., life satisfaction), suggesting potential subtypes of ASD that can be characterized by their personality profiles (Schwartzman et al., 2016). Expanding on these findings, a more recent study empirically identified personality subgroups in a clinical autistic youth sample with comorbid anxiety, and subgroup membership was a predictor of differential treatment response to two cognitive-behavioral therapy variants (Cho et al., *under review*).

The aforementioned findings demonstrate the early success of leveraging the FFM framework to better understand the heterogeneous nature of ASD. However, unlike its application in other clinical fields, the neurobiological substrates of the five personality domains in the ASD population have yet to be examined. For example, in psychopathy research, the literature suggests that two distinct pathways that together with disinhibition (low conscientiousness) may produce a psychopathic personality profile (meanness [low agreeableness, low affiliative extraversion, low neuroticism] vs. boldness [high extraversion and low neuroticism]), and that these pathways uniquely map onto the neural networks associated with disaffiliated agency (e.g., insula, medial prefrontal cortex) and threat sensitivity (e.g., amygdala), respectively (Patrick & Drislane, 2015). However,

personality-related autism research has been limited to behavioral findings. In order to advance the extant ASD personality literature, it is necessary to investigate the endophenotypes associated with personality domains in autistic individuals. Given the abnormal neural connectivity found in ASD (Hull et al., 2017; Lenroot & Yeung, 2013; Uddin et al., 2013), it is particularly important to understand these neural biomarkers of personality and how they resemble and differ from the general population. By doing so, it may be possible to further elucidate the degree to which findings in clinical personality research may be extended to the ASD population.

In the personality neuroscience literature, which still primarily consists of findings based on the general population, extraversion and neuroticism are the two personality domains that have been most researched (DeYoung et al., 2021; for a comprehensive review of the neuroimaging literature on all five personality domains, see Allen & DeYoung, 2017). Extraversion is defined as a "sensitivity to reward" and is highlighted by its two aspects: assertiveness and enthusiasm, which reflects the "wanting" and "enjoyment" of rewards, respectively (DeYoung, 2015). It is most strongly linked to the neurotransmitter dopamine and involves reward system neural circuitry that includes brain regions such as the ventromedial prefrontal cortex (ventromedial PFC), ventral and dorsal striatum, anterior cingulate cortex (ACC), and the substantia nigra/ventral tegmental area (SN/VTA), as well as the amygdala, due to its role in processing emotionally salient stimuli (Aghajani et al., 2014; Nostro et al., 2018; Pang et al., 2016). Alternatively, many studies have implicated the primary regions of Menon's triple network model of psychopathology (*central executive network* [CEN]: dorsolateral PFC, posterior parietal cortex [PPC]; *default mode network* [DMN]: medial PFC, posterior cingulate cortex [PCC]; *salience network* [SN]: ACC, insula; Menon, 2011) as the potential neural substrates of extraversion (Lei et al., 2013; Pang et al., 2017; Sampaio et al., 2014; Tian et al., 2018; Wei et al., 2011). While this model was originally proposed to synthesize and explain findings of the overlap between psychopathology and clinical diagnoses, these three large-

scale networks also could be seen as representing the neural underpinnings of higher-order functions involving social, cognitive, and emotion regulation processes, thus providing a set of potential neural correlates associated with personality variability. For example, Sampaio and colleagues found that extraversion was predicted by connectivity strength between the SN's ACC and right insula, suggesting that the SN's role in processing external information and attention allocation may be a mechanism associated with trait extraversion (2014).

On the other hand, neuroticism is marked by one's sensitivity to stress, conflict, and uncertainty, and the two aspects which encompass it are withdrawal and volatility (Allen & DeYoung, 2017). Withdrawal, represented by brain regions of the behavioral inhibition system (e.g., hippocampus; McNaughton & Gray, 2000), is affiliated with anxiety and depression traits and involves the passive avoidance or inhibition of goal-related pursuits (Cullen et al., 2014; Servaas, Riese, et al., 2013), while volatility, represented by the brain's fight-flight-freeze system (e.g., amygdala), is defined by traits related to irritability and emotional lability (DeYoung, 2015; Eckstein et al., 2017; Wang et al., 2018). Researchers have proposed a neurophysiological mechanism underlying neuroticism, characterized by hyperactivity in the affective regions of the brain (e.g., fear system) with under-regulation by the cognitive regions of the brain (Allen & DeYoung, 2017). Consistent with this hypothesis, recent findings regarding neuroticism implicate the SN and DMN's role in aversive stimuli sensitivity (Huggins et al., 2018; Nostro et al., 2018; Sampaio et al., 2014) and the CEN's role in emotion regulation (Fournier et al., 2017; Markett et al., 2013; Servaas, van der Velde, et al., 2013).

Given the abnormal functional connectivity that underlies the varied and complex presentations of ASD, the identification of personality-related neural markers is a critical step in the growth of the personality-related ASD research field. As such, the present study aimed to identify

the resting-state functional connections[2] (FCs) associated with personality domains in the ASD population. I only focused on extraversion and neuroticism for two reasons: first, these two domains are the most well-researched in personality neuroscience and will provide the most evidence to ground our present findings (DeYoung et al., 2021); second, group differences found between autistic and non-autistic individuals were largest for extraversion and neuroticism, which may indicate meaningful clinical variability for the two domains (Lodi-Smith et al., 2019). I hypothesized that, consistent with the literature on the general population, in the ASD sample, extraversion scores would be associated with resting-state functional connectivity (RSFC; i.e., connectivity strength) between the primary regions of the reward system (e.g., ventromedial PFC, striatum) and the triple networks (CEN: dorsolateral PFC, PPC; DMN: medial PFC, PCC; SN: ACC, insula), and neuroticism scores would be associated with RSFC between the amygdala, hippocampus, and the primary regions of the triple networks. Consistent with a central goal of personality-related autism research to delineate the phenotypic profiles within ASD, I conducted an exploratory analysis to investigate the association between extraversion/neuroticism-associated FCs with the remaining personality domains and extraversion/neuroticism-associated clinical characteristics (e.g., internalizing). Given the exploratory nature of this aim, no hypotheses were generated.

[2] *Resting-state functional connections are representative of node pairs with spontaneous blood-oxygen-level-dependent (BOLD) signals that demonstrate a temporal correlation, with the assumption that regions that activate together are functionally organized together (Woodward & Cascio, 2015).*

Methods and Materials

Participants

The present study included participants from the first wave of the University of California, Davis MIND Institute's ongoing cohort sequential *Neurodevelopment of Cognitive Control in Autism*

(R01MH106518) study, which examines the development of cognitive functioning in ASD from adolescence into early adulthood. The study screened 206 individuals (ages 12 to 22 years old) with and without ASD functioning in the average range of intelligence (ASD and TYP, respectively), all recruited from the greater Sacramento (California) area through study ads and flyers, clinicians, advocacy groups, and the MIND Institute's research participant database.

Eligibility criteria for autistic individuals included: (a) a confirmed clinical diagnosis of ASD via the DSM-5 Criteria Checklist and ADOS-2 (Autism Diagnostic Observation Schedule-Second Edition; Lord et al., 2012), and (b) having clinically significant social and communication problems (i.e., a total score greater or equal to 15 on the SCQ [Social Communication Questionnaire; Rutter et al., 2003]). In comparison, inclusion criteria for "typically-developing" (i.e., non-clinical) individuals were: (a) an SCQ score less than or equal to 11 and (b) no first degree relative with a history of ASD nor any reported Axis I psychopathology or neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD). Additionally, all participants must have had an estimated full-scale IQ equal or greater to 70 (computed from the WASI-II [Wechsler Abbreviated Scale of Intelligence-Second Edition; Weschler, 2011]), had no history of substance misuse, and were not on psychotropic medication at the time. Attention-deficit hyperactivity disorder medications in the ASD group were not an exclusion, but those medications were washed out prior to functional magnetic resonance imaging (fMRI) scans (i.e., 48-hour period).

Informed consent was obtained from either the participant or their parent/guardian. For youth participants, consent was obtained from their parent/guardian. For adult participants, some provided consent themselves, while others had consent provided by their parent/guardian. In all cases where the participants did not provide consent for themselves, assent was obtained. All procedures were approved by the UC Davis Institutional Review Board, and participants received

financial remuneration for their participation. A total of 157 participants had both personality and resting-state fMRI data, and seven cases were removed due to excessive motion during the structural or resting-state fMRI scan. Thus, the present study had a final sample size of 150 participants (TYP [n=77]: M_{Age}=16.92 years, SD=3.10; $M_{Full\text{-}scale\ IQ}$=110.17, SD=11.55; ASD [n=73]: M_{Age}=17.42 years, SD=3.00; $M_{Full\text{-}scale\ IQ}$=101.88, SD=14.14). See Table 1 for participant's demographic and measure scores.

Measures

The following measures were utilized to assess personality and its correlates in the current study. More complete descriptions of measures used in the study's participant screening process are reported in Appendix A of the Supplementary Materials.

Big Five Inventory – 2 (BFI-2)

The BFI-2 (Soto & John, 2017) is a 60-item self-report questionnaire designed to capture variation in personality characteristics across the Big Five domains (extraversion, agreeableness, conscientiousness, neuroticism, openness to experience). Participants are instructed to indicate on a 5-point Likert scale, ranging from "Disagree Strongly" to "Agree Strongly", the degree in which each statement (i.e., item) describes themselves (e.g., "Worries a lot." is a Neuroticism item). Each domain is assessed by 12 items and response scores are tabulated to generate a personality profile consisting of five domain scores, each ranging from 12 to 60. The questionnaire has exhibited strong psychometric properties across several languages and cultures (Denissen et al., 2019; Halama et al., 2020; Vedel et al., 2020). In this paper, lower-case terms (e.g., extraversion) were used when referring to personality constructs and upper-case terms (e.g., Extraversion) were used when referring to the BFI-2 domains. Reliability (Cronbach's alpha) for personality scores were acceptable,

ranging from .801 (Agreeableness) to .866 (Neuroticism) for TYP and .675 (Openness to Experience) to .849 (Conscientiousness) for ASD.

Child/Adult Behavior Checklist (CBCL/ABCL)

The CBCL and ABCL (Achenbach & Rescorla, 2001) are parent-reported assessments of psychopathology for individuals ages 6-18 and 18-59 years, respectively. The CBCL/ABCL are the most widely used measures of internalizing/externalizing research, serving as the primary measure for over 90% of identified studies within a period of 3 years (2012-2014) and across over 60 countries (Achenbach et al., 2016). Following recent recommendations to improve measurement fidelity (Achenbach et al., 2016), the present study used the specific subscales of internalizing (Depressive Problems, Anxious Problems, Withdrawn Problems, Somatic Complaints) and externalizing (Aggressive Behavior, Rule-Breaking Behavior) to assess extraversion/neuroticism-associated psychopathology. Age- and gender-corrected *T*-scores were used, and higher scores indicated increased psychopathology.

Rosenberg Self-Esteem Scale (RSE)

The RSE (Rosenberg, 1965) is a self-reported assessment of global self-esteem and is used as a measure of extraversion/neuroticism-associated impairment in the present study (α_{TYP}=.919, α_{ASD}=.918). Self-esteem is a particularly relevant construct in the present study given its association with extraversion and neuroticism (Amirazodi & Amirazodi, 2011; Joshanloo & Afshari, 2011), as well as social and mental health outcomes in autistic individuals (Cooper et al., 2017; Lu et al., 2015). The RSE has demonstrated strong psychometric properties and strong associations with clinical outcomes such as psychological and physical health (Robins et al., 2001; Sinclair et al., 2010). It has been widely used across different studies and in different cultures (Huang & Dong, 2012; Schmitt &

Allik, 2005), as well as the ASD population (e.g., Arwert & Sizoo, 2020; Chou et al., 2020). Scores can range from 10 to 40, with higher scores indicative of better self-esteem.

Resting-state fMRI Analysis Approach

Resting-state fMRI data were acquired while participants visually fixated on a white cross presented on a black background. Preprocessing was done in SPM 12 (Friston et al., 2014), and denoising was done in CONN 18 (Whitfield-Gabrieli & Nieto-Castanon, 2012) in accordance with recent guidelines to minimize motion artifacts (Ciric et al., 2017; Satterthwaite et al., 2019; see Appendix B for full resting-state fMRI acquisition, preprocessing, and denoising details). The present study's *a priori* focus on neural correlates underlying extraversion and neuroticism has implicated the reward system and "triple networks" as regions of interest (ROIs). The reward system consisted of 14 nodes defined in a reward system fMRI meta-analysis (Bartra et al., 2013), which has since been used in several other neuroimaging studies (e.g., Satterthwaite et al., 2015; Sharma et al., 2016). In the meta-analysis, these nodes were defined as specific coordinates; in the present study, rather than creating spheres around these coordinates, the identified nodes were defined using the Harvard-Oxford atlas (Desikan et al., 2006). The "triple networks" were defined using the 400-ROI parcellation of the Schaefer atlas, which consists of seven intrinsic functional networks derived from gradient-weighted Markov random field models of 1,489 participants' functional connectivity data (Schaefer et al., 2018; DMN: 79, CEN: 61, SN: 51 nodes). In total, 205 nodes were selected as *a priori* ROIs.

ROI-ROI (i.e., seed-to-seed) connectivity analyses were carried out in CONN using all *a priori* ROIs, resulting in 205*205 (42,025) seed-target pairs. All analyses included a conservative correction for multiple comparisons at the analysis-level, maintaining a false discovery rate (FDR) below threshold (q<.05), two-sided, so that findings were considered statistically robust. All analyses

also included age as a covariate to account for the wide age span in the sample. For the sake of comprehensiveness, an initial analysis was conducted to compare RSFC between the TYP and ASD groups without consideration of personality traits (i.e., two-sample *t*-test; *Analysis 1*). To address our research aims, we identified the extraversion and neuroticism-associated FCs independently for both the TYP and ASD groups (i.e., RSFC-personality regression; *Analysis 2*), producing four models: extraversion-associated FCs in TYP, extraversion-associated FCs in ASD, neuroticism-associated FCs in TYP, and neuroticism-associated FCs in ASD. These analyses were followed by a comparison of ROI-ROI pairs' association with Extraversion and Neuroticism *between* the TYP and ASD groups (i.e., one-way ANCOVA covariate interaction analyses; *Analysis 3*), producing two sets of identified FCs (one for Extraversion, one for Neuroticism). Functional connectivity maps of significant ROI-ROI pairs were then z-transformed into connectivity values for all participants. To further correct for the potentially confounding effects of motion on the results (i.e., significant FCs identified in Analyses 2 and 3), partial correlations (Spearman's rho [r_s]; controlling for participant mean motion [i.e., framewise displacement of in-scanner motion]) were examined.

Exploratory Analyses

Based on findings in Analyses 2 and 3, I examined the identified FCs' partial correlations (controlling for motion) with remaining personality domains (e.g., Extraversion, Agreeableness, Conscientiousness, and Openness to Experience for neuroticism-associated connections), autism severity (ADOS-CSS), and extraversion/neuroticism-associated behavioral measures (CBCL/ABCL, RSE). These exploratory analyses were conducted to determine whether the identified extraversion/neuroticism-associated connections were specific to only one personality domain and perhaps even linked to clinical characteristics. Significant partial correlations were followed up with mediation analyses to examine the potential mediation effects of personality domains on the

association between RSFC and clinical measure scores, after controlling for mean motion and autism severity, which could confound findings (IQ was not included as a covariate as it was not correlated with Extraversion or Neuroticism in either the TYP or ASD group). For example, if an identified connection was partially correlated with two personality domains and three clinical measures, six total mediation models were conducted. Mediation analyses followed Baron and Kenny (1986) guidelines, bootstrapping was used as a conservative test of indirect effects (Bollen & Stine, 1990; Shrout & Bolger, 2002), and effect sizes were calculated using Kenny (2018) guidelines (i.e., product of paths *a* and *b*'s partial correlations).

Results

An examination of zero-order correlations between sample demographics and BFI-2 domain scores revealed that participant age was significantly correlated with Extraversion (Spearman's ϱ [r_s]=-.239, p=.042) in the ASD group only. Full-scale IQ was significantly correlated with Openness to Experience (TYP: r_s=.352, p=.002; ASD: r_s=.271, p=.020) and Conscientiousness (ASD: r_s=-.278, p=.017). Autism severity was not significantly correlated with BFI-2 domains.

In Analysis 1 (i.e., two-sample *t*-test that was completed for the sake of comprehensiveness), I found nine FCs that differed (p-FDR<.05) between the TYP and ASD groups (see Appendix C and eTable 1 for a full report of these results). In Analysis 2, in contrast to the results of the extant literature, I found no FCs that were significantly associated with Extraversion in either the TYP or ASD groups. However, I found four FCs associated with Neuroticism in the ASD group, but none in the TYP group ([1] left parietal medial cortex-left retrosplenial cortex [SN-DMN], [2] left parietal medial cortex-right precuneus [SN-CEN], [3] left putamen-left intraparietal sulcus [RS-CEN], [4] left dorsal PFC-right mid-cingulate cortex [DMN-CEN]; also see Table 2 and Figure 1). In Analysis 3, I again found no FCs associated with Extraversion and one FC associated with Neuroticism (left

dorsal PFC-right mid-cingulate cortex), which was the same connection as one of the four found in the within-group Neuroticism ASD model in Analysis 2. As such, four total FCs were considered for further analyses.

Connections Associated with Neuroticism in the ASD Group

In Analysis 2, the Neuroticism model for the ASD group identified four significant FCs. In the ASD group, two connections (left parietal medial cortex-left retrosplenial cortex [SN-DMN]; left parietal medial cortex-right precuneus [SN-CEN]) were positively associated with Neuroticism, while two connections (left putamen-left intraparietal sulcus [RS-CEN]; left dorsal PFC-right mid-cingulate cortex [DMN-CEN]) were negatively associated with Neuroticism. Partial correlations (controlling for motion) between RSFC and Neuroticism remained significant for all four connections. In the Neuroticism model of Analysis 3, I identified the left dorsal PFC-right mid-cingulate cortex (DMN-CEN) FC, duplicating one of Analysis 2's Neuroticism findings. Specifically, this connection was negatively associated with Neuroticism in the ASD group (r_s=-.479; p<.001) and positively, but non-significantly, associated with Neuroticism in the TYP group (r_s=.207; p=.073).

Exploratory Analysis

As part of our exploratory aim, I examined the partial correlations (controlling for motion) between the four neuroticism-associated connections' RSFC (found in Analysis 2) and the remaining personality domains, autism severity, and extraversion/neuroticism-associated clinical characteristics (i.e., *internalizing*: Depressive Problems, Anxiety Problems, Withdrawn, Somatic Complaints; *externalizing*: Aggressive Behavior, Rule-Breaking Behavior; self-esteem) in the ASD group (Table 3). In summary, only one of the four connections (left dorsal PFC-right mid-cingulate cortex [DMN-CEN]) was associated with personality domains besides Neuroticism, suggesting that the three remaining connections are specifically associated with trait neuroticism in autistic individuals.

Namely, as detailed below, the left dorsal PFC-right mid-cingulate cortex FC was also positively associated with Extraversion and Conscientiousness (i.e., in the opposite direction of Neuroticism), which suggests that it may be more closely associated with the broader construct of internalizing (Tackett & Mullins-Sweatt, 2021).

In addition to Neuroticism, all four FCs were significantly associated with self-esteem (i.e., RSE score) in the expected directions. The two FCs positively associated with neuroticism were negatively associated with self-esteem, and the two FCs negatively associated with neuroticism were positively associated with self-esteem. Follow-up mediation analyses found that Neuroticism scores completely mediated the association between RSFC and RSE scores for all four connections, after controlling for motion and autism severity which could confound findings (Table 4). These findings indicate that the association between these four FCs and self-esteem can be fully attributed to the connections' association with neuroticism, suggesting these connections as potential neural markers of neuroticism and that neuroticism is a potent risk factor for low self-esteem in autistic individuals.

Next, the left putamen-left intraparietal sulcus (RS-CEN) FC within the ASD group was also partially correlated with CBCL/ABCL Depressive Problems (r_s=-.423, p<.001), Somatic Complaints (r_s=-.404, p=.001), and Aggressive Behavior (r_s=-.268, p=.026). Neuroticism scores partially mediated the association between RSFC and Depressive Problems (controlling for motion and autism severity) but not the association between RSFC and Somatic Complaints or Aggressive Behavior. This suggests that, for autistic individuals, this FC may be specifically associated with traits of neuroticism that promotes the affective aspects of internalizing (i.e., depression) but not traits of neuroticism that underlie the physical elements of internalizing (i.e., somatic) or aggressive behavior (a form of externalizing psychopathology).

Finally, the left dorsal PFC-right mid-cingulate cortex (DMN-CEN) FC within the ASD group was also partially correlated with Extraversion (r_s=.293, p=.013), Conscientiousness (r_s=.349, p=.003), and CBCL/ABCL Depressive Problems (r_s=-.253, p=.036). Conscientiousness and Neuroticism scores both independently and completely mediated the association between RSFC and Depressive Problems and RSE (controlling for motion and autism severity), but Extraversion did not mediate the association between RSFC and either measure. These findings implicate this FC as a potential neural marker of positive mental health outcomes for autistic individuals, in which a stronger connection is associated with lower neuroticism and higher conscientiousness, and in turn results in less depressive problems and higher self-esteem.

Discussion

The present study aimed to identify the neural substrates of trait extraversion and neuroticism in the ASD population. Specifically, I conducted an ROI-ROI analysis to examine the association between RSFC (i.e., connectivity strength) and self-reported scores on a Big Five personality measure for an ASD sample as well as a TYP sample that served as a reference group. I did not find extraversion-associated connections in either group but found four neuroticism-associated connections in the ASD group. In two of these connections, RSFC were positively associated with Neuroticism (i.e., as connectivity strength increased, Neuroticism score increased) and two were negatively associated with Neuroticism. In my exploratory analysis, I found that the four neuroticism-associated FCs in the ASD group were also correlated with clinical characteristics such as self-esteem and internalizing symptoms, and these associated were mediated by neuroticism scores. In summary, while the present findings did not confirm my hypothesis about extraversion-associated connections in autistic individuals, I found FCs associated with neuroticism that spanned the reward system and triple networks (but not the amygdala and hippocampus) in autistic

individuals. In the remainder of this section, I will discuss the four neuroticism-associated FCs in context of the extant personality neuroimaging literature, as well as the potential mechanisms through which they may be associated with neuroticism in autistic individuals.

Analyses 2 and 3 both identified the left dorsal PFC-right mid-cingulate cortex FC, which are parts of the DMN and CEN, respectively, as a connection negatively associated with trait neuroticism. In the personality neuroscience literature, the dorsal PFC is considered a key region in the behavioral inhibition system, which has been strongly linked to the withdrawal aspect of neuroticism (i.e., anxiety, depression, passive avoidance, and inhibition of goal-related pursuits; Kennis et al., 2013; McNaughton & Corr, 2004). Research suggests this brain region is involved in the top-down cognitive control of emotion, and as such, could play an important role in the manifestation of trait neuroticism (Cremers et al., 2010; Ozawa et al., 2014; Philiastides et al., 2011). Specifically, accumulating evidence suggests that high functional connectivity between the dorsal PFC and cingulate regions is likely helpful in regulating negative emotionality (Hofmann et al., 2012; Servaas, van der Velde, et al., 2013; Touroutoglou et al., 2020). Similarly, the mid-cingulate cortex is involved in emotion processing and regulation (Hofmann et al., 2012; Ochsner & Gross, 2005) by directing increased attention in anticipation of negative stimuli (DeYoung et al., 2010; Drabant et al., 2011; Servaas, van der Velde, et al., 2013). In summary, it may seem that autistic individuals with stronger RSFC between these two nodes are more equipped to respond to ambiguous or aversive environmental cues, and as such, present a less neurotic personality profile.

Next, RSFC between the left putamen-left intraparietal sulcus, which are parts of the RS and CEN, respectively, was also negatively associated with trait neuroticism in the ASD sample. The putamen has been positively associated with reward-related processing and learning (Ghandili & Munakomi, 2021; Kunimatsu et al., 2019; Muranishi et al., 2011). It is also generally associated with

trait neuroticism (Fuentes et al., 2012; Kumari et al., 2007); however, the directionality of this association appears to be contextual (Coen et al., 2011). In a quantitative meta-analysis on emotion processing (Servaas, van der Velde, et al., 2013), left putamen activity was found to be negatively correlated with neuroticism when participants were presented negative stimuli (vs neutral stimuli). On the other hand, the intraparietal sulcus is a region that may be involved in visual attention, working memory, response inhibition, as well as learning rules (Bray et al., 2015; Osada et al., 2019; Sui et al., 2015). However, while there have been some findings suggesting that the intraparietal sulcus may be associated with social anxiety symptoms (through mechanisms pertaining to abnormal attention and mental representation of the social environment; e.g., Irle et al., 2014; Jung et al., 2018), I did not find previous studies that have linked the intraparietal sulcus to trait neuroticism. Functional connectivity strength between these two nodes may be indicative of reward-related learning and response inhibition to emotionally-salient stimuli. The present findings support the extant literature which suggests atypical reward processing as an important component of trait neuroticism, and on a more clinical level, depressive symptoms (Bakker et al., 2018; Knutson et al., 2008; Ng et al., 2019).

Conversely, RSFC between the left parietal medial cortex-left retrosplenial cortex and the left parietal medial cortex-right precuneus were both positively associated with trait neuroticism. Both connections include the left parietal medial cortex, a large region in the SN that includes several neural substrates (e.g., precuneus, PCC) and has been linked to functions such as memory recall, attention, perspective-taking, and self-reflection (Bzdok et al., 2015; Johnson et al., 2009; Silson et al., 2019). Specifically, the identified parietal medial cortex node straddles the precuneus, a region involved in both the SN and CEN that is suggested to be involved in self-awareness, episodic memory, conscious information processing, and visuospatial attention (Freton et al., 2014; Vogt & Laureys, 2005; Wenderoth et al., 2005). Several personality neuroimaging studies have suggested the

precuneus as a part of the behavioral inhibition system, highlighting its negative association with neuroticism in structural and task-based functional imaging studies (Coen et al., 2011; Fuentes et al., 2012; Servaas, van der Velde, et al., 2013). Similarly, activation in the retrosplenial cortex, a region in the DMN related to self-referential processing and episodic memory (especially regarding emotionally salient stimuli; Chrastil, 2018; Maddock, 1999; Vann et al., 2009), has also been found to be negatively correlated with neuroticism during the "worry trials" (vs neutral trials) of a mood induction paradigm (Servaas et al., 2014). In fact, this study also found increased functional connectivity between the precuneus and retrosplenial cortex during the worry trials, a finding that parallels the present study's two FCs that were positively associated with Neuroticism scores. In summary, there is a common theme of memory, attention, and self-reflection across these three identified nodes. A possible explanation of the present findings is that, within the ASD population, abnormal RSFC (i.e., overconnectivity) in these two connections may represent a mechanism underlying repetitive negative thinking and over-sensitivity to negative stimuli, a finding consistent with depression research (Cheng et al., 2018; Corcoran et al., 2018; Johnson et al., 2009). It is also worth noting that the aforementioned nodes span all three of Menon's triple networks, converging with the extant literature which suggests that abnormal connectivity between these networks may underlie psychopathology (which, in this instance, are internalizing characteristics that were mediated by trait neuroticism).

Finally, the partial correlations and mediation models in the exploratory analysis provide additional insights into the four neuroticism-associated FCs. With the exception of the left dorsal PFC-right mid-cingulate cortex FC, the identified connections were correlated with Neuroticism but not the remaining four personality domains. This provides initial evidence that the identified connections are specifically linked to the neuroticism personality domain and not representative of neural substrates for a general personality factor (van der Linden et al., 2010). In contrast, the RSFC

of the left dorsal PFC-right mid-cingulate cortex connection was less specific to Neuroticism in that it was also positively associated with trait extraversion and conscientiousness, which, according to the personality neuroscience literature, maps onto the trait indicators of low internalizing psychopathology (i.e., internalizing is associated with high neuroticism, low extraversion, and low conscientiousness; Tackett & Mullins-Sweatt, 2021). This suggests that this FC may not only be a neural marker of low neuroticism but may also serve a broader role in the inhibition of internalizing characteristics. In addition, while the four neuroticism-associated FCs were also correlated with clinical characteristics (e.g., self-esteem and internalizing symptoms), these associations were either partially or fully mediated by Neuroticism scores. This provides further evidence that these FCs are primarily linked to trait neuroticism, and it is through this linkage in which the neural substrates appear to demonstrate associations with various clinical characteristics.

The present findings contribute to the ongoing research efforts of the clinical personality field. In particular, the neuroimaging results here provide additional evidence of ASD's fit within personality science's Hierarchical Taxonomy of Psychopathology (HiTOP) framework (Kotov et al., 2017), which has primarily been used to examine mood and personality disorders. The neural markers of neuroticism in the study's ASD sample seem to converge with the broader extant personality neuroscience literature on neuroticism. However, more research needs to be conducted to better understand the extent in which the clinical overlap between ASD and other disorders can be contextualized within a personality science framework. More importantly, this study contributes to the broader research goal of personality-related autism research, which can be summarized as the improved conceptualization and treatment of ASD. These initial findings of neuroticism-associated FCs and their associations with certain clinical characteristics (i.e., internalizing, self-esteem) in the ASD population may be particularly relevant in clinical practice, given that personality traits and profiles have shown to be predictors in psychotherapy (Bucher et al., 2019; Cho et al., *under review*)

and neuroticism has been a successful intervention target in clinical settings (Barlow et al., 2014; Sauer-Zavala et al., 2017). As this research subfield continues to grow, it may be better able to complement traditional diagnostic systems (e.g., DSM-5) to understand the heterogeneity within ASD and its phenotypic overlap with other clinical disorders.

This study serves as the first neuroimaging study in the emerging field of personality-related autism research, which aimed to tackle questions about the neural substrates of personality in the ASD population. While I did not find extraversion/neuroticism-associated FCs in the TYP group, I found neuroticism-associated connections in the ASD group that appear to map onto the extant personality neuroimaging literature. This suggests that, while there are pronounced personality trait differences between autistic and non-autistic individuals (Lodi-Smith et al., 2019) as well as within the ASD population (Cho et al., *under review*; Schwartzman et al., 2016), the neurocircuitry which underlie neuroticism do not differ between those with and without ASD. These findings provide initial evidence that the neurobiological underpinnings of personality science's FFM framework could be extended to the ASD population as well. Furthermore, the present study found that most, but not all, associations between identified connections and clinical measures (e.g., self-esteem, internalizing) were mediated by neuroticism. This may be an important point of consideration in personality-related autism research when using personality traits to study individual differences in clinical profiles (i.e., the degree to which differences in personality traits map onto differences in clinical characteristics).

Several limitations must be considered. First, neither the ASD nor TYP groups are fully representative of the ASD and general populations, respectively. Namely, the ASD group had relatively low incidence of comorbid anxiety disorders (7%, based on clinical interviews, versus 40% as estimated in van Steensel et al., 2011) and the TYP group also presented a clinical profile with

relatively few symptoms (e.g., anxiety, ADHD symptoms). This can be partially attributed to the study recruitment process, which opted not to recruit individuals who were taking psychotropic medications as it may confound with neuroimaging results (Linke et al., 2017). Furthermore, the study sample adhered to an IQ inclusion criterion of 70 or higher, was limited to an age range of 12 to 22 years old, and primarily consisted of White/Caucasian participants from high socioeconomic status backgrounds. Second, there was a difference of in-scanner motion between the ASD and TYP groups. However, this is primarily a concern for cross-group analyses (i.e., Analyses 1 and 3, but not Analysis 2). Furthermore, while the present study controlled for motion in the denoising step, partial correlations, and mediation analyses, in-scanner motion was correlated with participants' Neuroticism score. This serves as a point of debate regarding the tradeoff between motion correction (minimizing Type I error) and possibly eliminating the neural signal of neuroticism (Type II error). Finally, the ASD population demonstrates considerable heterogeneity in individuals' RSFC, which may mask the relevant signals of personality endophenotypes in the ASD group. In other words, the neural correlates of personality domains may differ between autistic individuals and/or potential subtypes. Given this and the number of correlates involved in the analyses of extraversion and neuroticism, a larger sample is required to ensure that the study is appropriately powered.

The present study provides preliminary evidence of RSFC that is associated with neuroticism. These findings seem to converge with the extant personality neuroimaging literature on the general population. Future studies should aim to examine the neural correlates of the remaining three personality domains (agreeableness, conscientiousness, and openness to experience) in the ASD population. Future studies should also aim to replicate and extend these findings in other age groups within the ASD population and in a more representative sample in terms of race/ethnicity, SES, cognitive ability, and verbal ability.

Table 1

Sample Demographics and Measure Scores

	TYP Group *n*=77	ASD Group *n*=73	Groupwise Comparison
	Count (Proportion)	Count (Proportion)	
Sex (Male)	60 (77.9%)	58 (79.5%)	$\chi^2(1, 150)=.052$, $p=.819$
Ethnic Background			
Asian	10 (13.0%)	7 (9.6%)	
Black / African-American	3 (3.9%)	1 (1.4%)	
Latino/a / Hispanic	6 (7.8%)	13 (17.8%)	
White / Caucasian	42 (54.5%)	37 (50.7%)	
Multiracial	16 (20.8%)	15 (20.5%)	
Asian + Black / African-American	1 (1.3%)	0 (0.0%)	
Asian + Latino/a / Hispanic	1 (1.3%)	1 (1.4%)	
Asian + White / Caucasian	3 (3.9%)	2 (2.7%)	
Black / African-American + Latino/a / Hispanic	1 (1.3%)	1 (1.4%)	
Black / African-American + White / Caucasian	1 (1.3%)	6 (8.2%)	
White / Caucasian + American Indian or Alaskan Native	5 (6.5%)	5 (6.8%)	
3+ Ethnicities	4 (5.2%)	0 (0.0%)	
	Mean (*SD*)	Mean (*SD*)	
Age (Years)	16.92 (3.10)	17.42 (3.00)	$t(148)=-1.008$, $p=.315$
WASI-II			
Full-Scale IQ	110.17 (11.55)	101.88 (14.14)	$t(148)=3.943$, $p<.001$
Verbal Comprehension Index	106.13 (12.31)	97.53 (14.14)	$t(148)=3.977$, $p<.001$
Perceptual Reasoning Index [a]	111.82 (13.02)	106.34 (17.21)	$t(133.95)=2.189$, $p=.030$
ADOS-2			
Calibrated Severity Score	--	7.71 (1.65)	--
Social Affect	--	7.78 (1.42)	--
Restricted and Repetitive Behaviors	--	7.04 (2.28)	--
SCQ Total [a]	2.91 (3.10)	21.77 (5.23)	$t(109.86)=-26.284$, $p<.001$
Child/Adult Behavior Checklist			

Depressive Problems [a]	53.23 (5.54)	61.66 (8.48)	$t(117.53)=-7.034$, $p<.001$
Anxiety Problems [a]	52.04 (3.55)	57.54 (8.20)	$t(92.56)=-5.180$, $p<.001$
Withdrawn [a]	53.77 (5.60)	62.57 (8.45)	$t(118.59)=-7.336$, $p<.001$
Somatic Complaints [a]	53.07 (5.05)	58.31 (9.18)	$t(105.63)=-4.222$, $p<.001$
Aggressive Behavior [a]	51.31 (2.75)	55.07 (5.69)	$t(97.93)=-5.017$, $p<.001$
Rule-Breaking Behavior [a]	51.43 (2.46)	54.10 (4.83)	$t(100.96)=-4.154$, $p<.001$
Rosenberg Self-Esteem Scale	32.89 (5.91)	29.74 (6.17)	$t(141)=3.127$, $p=.002$
Big Five Inventory – 2			
Extraversion	42.64 (7.93)	34.78 (8.75)	$t(148)=5.768$, $p<.001$
Agreeableness	48.00 (7.03)	46.37 (7.42)	$t(148)=1.382$, $p=.169$
Conscientiousness	44.29 (8.31)	40.05 (8.76)	$t(148)=3.039$, $p=.003$
Neuroticism	28.08 (9.00)	32.85 (8.19)	$t(148)=-3.391$, $p=.001$
Openness to Experience	47.08 (7.63)	44.95 (6.79)	$t(148)=1.802$, $p=.074$

Note. [a] = The measure had a significant Levene's Test for equality of variances and so the reported pairwise comparison is based on the Welch approximation *t*-test (i.e., does not assume equal variance). WASI-II=Wechsler Abbreviated Scale of Intelligence – Second Edition, ADOS-2=Autism Diagnostic Observation Schedule, Second Edition, SCQ=Social Communication Questionnaire.

Table 2

Neuroticism-associated ROI-ROI Functional Connections in the ASD Group (Analysis 2)

Functional Connection	Associated Functional Network	MNI Coordinates	Test Statistic	Partial r_s
Left parietal medial cortex-left retrosplenial cortex	SN-DMN	(-6, -48, 56) (-14, -60, 18)	$t(70)=5.01$, p-FDR=.042	.451
Left parietal medial cortex-right precuneus	SN-CEN	(-6, -48, 56) (16, -64, 28)	$t(70)=4.82$, p-FDR=.042	.467
Left putamen-left intraparietal sulcus	RS-CEN	(-20, 6, -6) (-34, -62, 48)	$t(70)=-4.89$, p-FDR=.042	-.363
Left dorsal prefrontal cortex-right mid-cingulate cortex	DMN-CEN	(-4, 52, 28) (4, 2, 30)	$t(70)=-4.89$, p-FDR=.042	-.479

Note. CEN=central executive network, DMN=default-mode network, SN=salience network, RS=reward system. FDR=false-discovery rate, r_s=Spearman's rho. All four reported functional connections were identified by regressing resting-state functional connectivity (i.e., connectivity strength) on Neuroticism in the ASD group, controlling for age. The one-way ANCOVA covariate interaction analysis of Neuroticism duplicated the identification of the left dorsal prefrontal cortex-right mid-cingulate cortex connection (Analysis 3 findings). MNI coordinates are reported in the order of which the two ROIs are presented in each functional connection. Reported correlations are partial correlations between z-transformed connectivity values and Neuroticism scores in the ASD group, controlling for motion.

Table 3

Spearman Partial Correlations (Controlling for Motion) of Neuroticism-associated Functional Connections (Analysis 2) with Personality Domains and Clinical Measures in the ASD Group

	Functional Connection			
	Left parietal medial cortex-left retrosplenial cortex (SN-DMN)	Left parietal medial cortex-right precuneus (SN-CEN)	Left putamen-left intraparietal sulcus (RS-CEN)	Left dorsal prefrontal cortex-right mid-cingulate cortex (DMN-CEN)
Big Five Inventory – 2				
Extraversion	-.193	-.214	.078	.293 [a]
Agreeableness	.016	.034	.003	.100
Conscientiousness	-.034	-.101	.217	.349 [b]
Neuroticism	.451 [c]	.467 [c]	-.363 [b]	-.479 [c]
Openness to Experience	-.050	-.011	.093	.143
ADOS-2 CSS	-.009	-.147	-.041	.047
Child/Adult Behavior Checklist				
Depressive Problems	.113	.113	-.423 [c]	-.253 [a]
Anxious Problems	.091	.117	-.112	-.030
Withdrawn Problems	.050	.023	-.230	-.178
Somatic Complaints	.080	.031	-.404 [b]	-.124
Aggressive Behavior	.013	.064	-.268 [a]	-.018
Rule-Breaking Behavior	.030	.163	-.189	.062
Rosenberg Self-Esteem Scale	-.256 [a]	-.372 [b]	.345 [b]	.301 [a]

Note. [a] <.05, [b] <.01, [c] <.001. CEN=central executive network, DMN=default-mode network, SN=salience network, RS=reward system. ADOS-2=Autism Diagnostic Observation Schedule, Second Edition, CSS=Calibrated Severity Score.

Table 4

Mediation Effects of Personality Domains between Functional Connections (Analysis 2) and Clinical Measures in the ASD Group, Controlling for Motion and Autism Severity

			Model 1	Model 2		Bootstrapping (Test of Indirect Effect)				
Functional Connection (X)	Personality Domain (M)	Clinical Measure (Y)	Path *a* X->M	Path *b* M->Y	Path *c'* X->Y	*ab*	95% CI	*c'*	95% CI	Effect Size
Left parietal medial cortex-left retrosplenial cortex (SN-DMN)	Neuroticism	RSE	12.720 [c]	-.506 [c]	1.004	-6.241 [c]	[-9.68 - -2.93]	1.004	[-3.36 - 5.09]	.116
Left parietal medial cortex-right precuneus (SN-CEN)	Neuroticism	RSE	11.925 [c]	-.470 [c]	-.857	-5.646 [c]	[-9.32 - -2.76]	-.857	[-4.06 - 2.46]	.183
Left putamen-left intraparietal sulcus (RS-CEN)	Neuroticism	CBCL/ABCL Dep. Prob.	-14.256 [c]	.468 [c]	-9.503 [a]	-6.239 [c]	[-10.87 - -2.39]	-9.503 [b]	[-19.01 - -2.15]	.155
		CBCL/ABCL Som. Com.	-14.256 [c]	.211	-11.371 [a]	-2.809	[-7.88 - 1.01]	-11.371 [b]	[-21.56 - -3.24]	.148
		CBCL/ABCL Agg. Beh.	-14.256 [c]	.160	-5.331	-2.131	[-4.69 - -0.17]	-5.331 [a]	[-11.75 - -0.07]	.099
		RSE	-14.256 [c]	-.447 [c]	3.791	5.978 [c]	[2.69 - 9.72]	3.791	[-1.34 - 9.47]	.125
Left dorsal prefrontal cortex-right mid-cingulate cortex (DMN-CEN)	Neuroticism	CBCL/ABCL Dep. Prob.	-14.832 [c]	.604 [c]	2.106	-9.14 [c]	[-15.18 - -4.28]	2.106	[-4.98 - 7.74]	.121
		RSE		-.511 [c]	-1.711	7.836 [c]	[4.26 - 11.72]	-1.711	[-6.07 - 2.88]	.146

Conscientiousness	CBCL/ABCL Dep. Prob.	12.746 [b]	-.453 [c]	-.979	-6.054 [b]	[-10.72 - -2.30]	-.979	[-9.33 - 6.03]	.087
	RSE		.208 [a]	3.368	2.757 [a]	[0.28 - 5.54]	3.368	[-2.49 - 9.65]	.105
Extraversion	CBCL/ABCL Dep. Prob.	9.437 [a]	-.256 [a]	-4.599	-2.435	[-6.55 - 0.41]	-4.599	[-12.56 - 2.58]	.074
	RSE		.359 [c]	2.839	3.286	[-0.04 - 7.97]	2.839	[-2.21 - 8.06]	.090

Note. [a] <.05, [b] <.01, [c] <.001. CEN=central executive network, DMN=default-mode network, SN=salience network, RS=reward system. RSE=Rosenberg Self-Esteem Scale, Dep. Prob.=Depressive Problems, Som. Com.=Somatic Complaints, Agg. Beh.=Aggressive Behavior. Effect size is calculated as the product of paths *a* and *b*'s partial correlations (i.e., connection strength with personality domain score and clinical measure score), controlling for motion and autism severity (small effect size: .01, medium: .09, large: .25; Kenny, 2018).

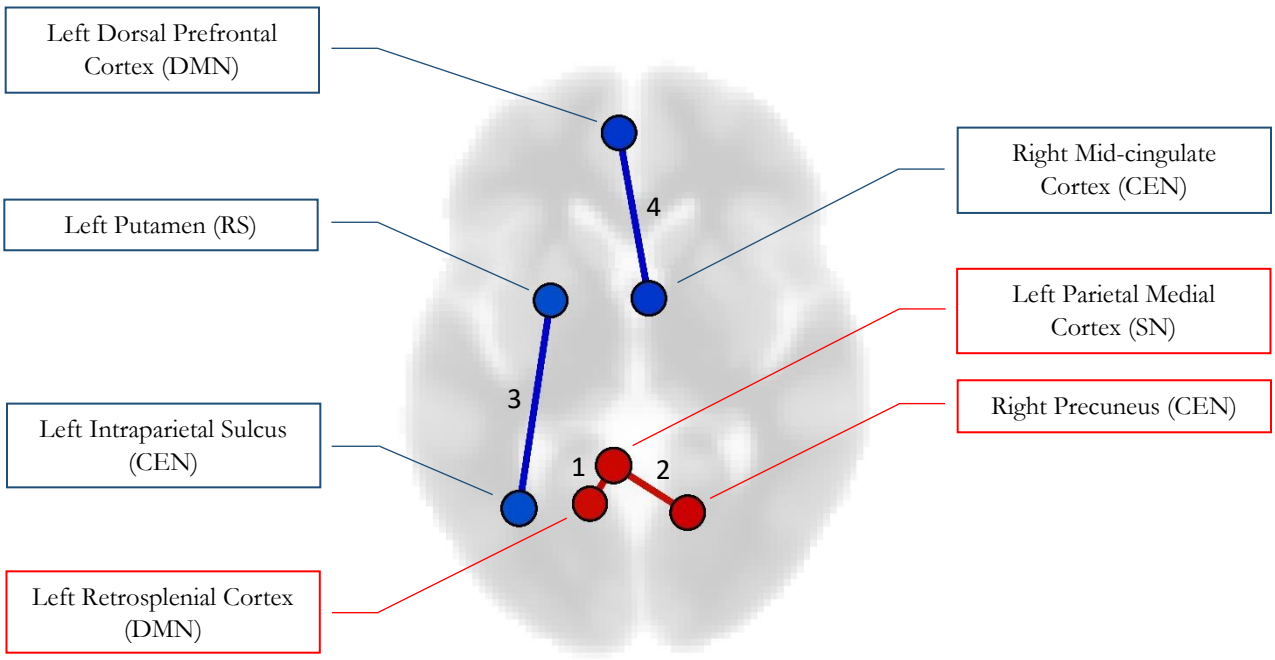

Figure 1. Four functional connections in the ASD group were significantly associated with Neuroticism (Analysis 2). Connections 1 and 2 demonstrated a positive association with Neuroticism, while connections 3 and 4 demonstrated a negative association with Neuroticism. (1) $t(70)=5.01$, p-FDR=.042, (2) $t(70)=4.82$, p-FDR=.042, (3) $t(70)=-4.89$, p-FDR=.042, (4) $t(70)=-4.89$, p-FDR=.042. CEN=central executive network, DMN=default-mode network, SN=salience network, RS=reward system. FDR=false-discovery rate.

Appendix A – Study Inclusion/Exclusion Criteria Measures

Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II)

The WASI-II (Wechsler, 2011) is a brief intelligence assessment designed for individuals ages six to 90 years old. It serves as a concise abbreviation of both the WISC-IV (Wechsler Intelligence Scale for Children, Fourth Edition; Wechsler, 2003) and WAIS-IV (Wechsler Adult Intelligence Scale, Fourth Edition; Wechsler, 2008). The WASI-II is composed of four subtests: Block Design, Vocabulary, Matrix Reasoning, and Similarities. Together, these subtests generate an estimated full-scale IQ score (FSIQ), as well as a Verbal Comprehension Index score (verbal IQ, based on Vocabulary and Similarities performance) and a Perceptual Reasoning Index score (nonverbal IQ, based on Block Design and Matrix Reasoning performance). Notably, the WASI-II presents well-established validity and reliability (McCrimmon & Smith, 2013) and is a common measure of general intelligence in autism research (Klinger et al. , 2018). All participants had to have a FSIQ score of 70 or greater to be eligible for study.

Autism Diagnostic Observation Schedule – Second Edition (ADOS-2)

The ADOS-2 (Lord et al., 2012) is a semi-structured observational assessment administered by trained, licensed clinical psychologists to elicit social interaction, language samples, and potential restricted or repetitive behaviors as a measure of ASD symptom severity and diagnostic classification. Considered a gold standard clinical tool in autism research, different modules are selected by the clinician based on the participant's language ability (among other variables), with each module demonstrating robust validity and reliability (Bastiaansen et al., 2011; Fusar-Poli et al., 2017; Gotham et al., 2007). Additionally, the ADOS-2 also provides a calibrated severity score (CSS) which measures relative symptom severity, as well as specific severity scores for social affect (SA) and restricted and repetitive behaviors (RRB). Autistic participants were required to have a total

score equal or greater than 7.

Social Communication Questionnaire (SCQ)

The SCQ (Rutter et al., 2003) is a 40-item, parent-reported autism screening tool used to assess level of social communication impairment. Traditionally, a cutoff score of 15 (or greater) indicates a clinical diagnosis of ASD. However, several studies have indicated that a cutoff score of 11 maximizes sensitivity and specificity (Allen et al., 2007; Oosterling et al., 2010; Wiggins et al., 2007), and the SCQ is best interpreted in conjunction with the ADOS-2 (Corsello et al., 2007). The SCQ has shown strong sensitivity and moderate specificity (0.88 and 0.72, respectively; Chandler et al., 2007) and has proven to perform well compared to several other ASD rating scales (Norris & Lecavalier, 2010). Typically-developing participants must score less than or equal to 11 to qualify for the study, while ASD participants must score 15 or higher.

Appendix B – Resting-state fMRI Data Acquisition, Preprocessing, and Denoising Methods

Resting-state fMRI Data Acquisition

MRI data were acquired on a 3T Siemens TIM Trio scanner with a 32-channel phased-array head coil. Sagittal T1-weighted structural images were acquired using an MPRAGE sequence (duration=6:02, TR=2530 ms, TE=3.5 ms, slice thickness=1 mm, FOV=256 mm, voxel size=1 mm iso, PAT mode=GRAPPA, PE=2). Functional T2*-weighted images were acquired during the resting-state run using an echo-planar imaging (EPI) sequence (duration=5:04, TR=2000, TE=24, FOV=224, voxel size=3.5 mm iso, flip angle=90 degrees, EPI factor=64). By default, the scanner automatically removes the first three volumes of each scan sequence. During rs-fMRI acquisition, participants were instructed to lie still, stay awake, and relax while maintaining eye fixation on a white cross presented on a black background.

Preprocessing

Data were preprocessed using the Statistical Parametric Mapping (SPM 12; Friston et al., 2014) software. Steps included: (1) field map (distortion) correction, (2) slice timing correction, (3) functional realignment and unwarping, (4) functional reorientation (i.e., centering to origin), (5) co-registration of functional and structural images, (6) segmentation and normalization, (7) motion artifact detection via the ART Toolbox, and (8) functional smoothing (8 mm FWHM), in this particular order. Specifically, outlier volumes were identified as any volume with linear motion over 0.5 mm. As noted in the Participants section, all cases with excessive motion (>50% data loss) were excluded from analysis (Hogeveen et al., 2018; Ray et al., 2014).

Denoising

Data were denoised using the CONN Functional Connectivity Toolbox (CONN 17;

Whitfield-Gabrieli & Nieto-Castanon, 2012) in accordance with recent denoising guidelines to minimize motion artifacts (Ciric et al., 2017; Satterthwaite et al., 2019). Specifically, the present study's denoising pipeline included (a) six realignment parameters (three translations, three rotations) and their first-order derivatives, (b) two physiological time series: mean white matter and mean cerebrospinal fluid (WM/CSF) signals, and (c) effect of rest, totaling to 24 parameters (excluding outlier volume parameters). The pipeline also included linear detrending, temporal band-pass filtering (0.01-0.08 Hz), and despiking of outlier volumes after regression.

Appendix C – Preliminary Findings: ASD and TYP Group Differences in Resting-state Functional Connectivity (Analysis 1)

Preliminary analysis included a two-sample *t*-test comparison between the resting-state functional connectivity of the ASD group versus the TYP group, controlling for age. Among the *a priori* networks (namely, the central executive network [CEN], default-mode network [DMN], salience network [SN], and reward system [RS]), nine significant connections demonstrated overconnectivity in ASD versus TYP. Two connections involved the temporal lobe: (1) left temporal lobe-left putamen (DMN-RS), $t(147)=4.80$, p-FDR=.028; (2) left temporal lobe-left pallidum (DMN-RS), $t(147)=5.29$, p-FDR=.009. Three connections involved the nucleus accumbens: (3) right nucleus accumbens-left insula (RS-SN), $t(147)=4.64$, p-FDR=.041; (4 and 5) right nucleus accumbens-left ventral prefrontal cortex (RS-DMN), $t(147)=4.79$, p-FDR=.028 and $t(147)=4.44$, p-FDR=.047 (the right nucleus accumbens was associated with two nodes of the left ventral prefrontal cortex). Three connections involved the precuneus/posterior cingulate cortex (i.e., preC/PCC): (6) right preC/PCC-left lateral prefrontal cortex (DMN-CEN), $t(147)=4.50$, p-FDR=.047; (7 and 8) left preC/PCC-right lateral ventral prefrontal cortex (DMN-CEN), $t(147)=4.53$, p-FDR=.047 and $t(147)=4.39$, p-FDR=.050. One connection was between the (9) left intraparietal sulcus-right parietal medial cortex (CEN-SN), $t(147)=4.46$, p-FDR=.047. These connections' partial correlations (controlling for motion) with the BFI-2 personality domains and clinical measures within the study design (i.e., ADOS-CSS, CBCL/ABCL internalizing and externalizing subscales, RSE) are reported in eTable 1. While informative, these findings were not relevant to our main research question, and as such, were not considered in further analyses.

eTable 1

Spearman Partial Correlations (Controlling for Motion) of Analysis 1 Functional Connections with Personality Domains and Clinical Measures

	Functional Connection								
	1	2	3	4	5	6	7	8	9
TYP Group (*n*=77)									
Big Five Inventory – 2									
Extraversion	.061	.168	.023	.025	-.013	-.008	-.101	-.030	-.149
Agreeableness	-.056	-.263 [a]	-.008	-.120	-.168	-.197	-.090	.065	-.238 [a]
Conscientiousness	-.199	-.240 [a]	.060	-.078	-.168	-.131	-.041	.169	-.226
Neuroticism	.040	.145	.075	-.039	-.136	.218	.030	-.039	.195
Openness to Experience	-.211	-.177	-.029	.033	.003	-.057	.076	.042	-.110
ADOS-2 CSS	--	--	--	--	--	--	--	--	--
Child/Adult Behavior Checklist									
Depressive Problems	.211	.178	.005	-.050	-.071	.132	-.060	-.264 [a]	.086
Anxious Problems	.065	.105	-.036	.052	.019	-.081	-.118	-.119	.127
Withdrawn Problems	.205	.06	.067	-.029	-.121	.189	-.086	-.164	.131
Somatic Complaints	.233	.114	.088	-.067	.011	.063	.029	-.245 [a]	-.030
Aggressive Behavior	.024	.087	.245 [a]	-.069	.056	.104	.077	-.051	.018
Rule-Breaking Behavior	.142	.112	.186	-.065	-.052	.024	-.173	-.253 [a]	.115
Rosenberg Self-Esteem Scale	.024	-.026	-.122	.029	-.039	-.259 [a]	-.114	.117	-.233 [a]
ASD Group (*n*=73)									
Big Five Inventory – 2									
Extraversion	.117	.007	-.018	-.136	-.105	.006	-.199	-.164	.012
Agreeableness	.143	.110	.050	.021	-.133	.127	-.030	.109	-.073

Conscientiousness	.071	-.062	.102	.060	-.080	.032	.001	.087	.021
Neuroticism	.238 [a]	.234 [a]	-.022	.062	.038	-.031	.098	.024	.113
Openness to Experience	.115	.117	.052	.053	.086	.066	-.072	.033	-.032
ADOS-2 CSS	.070	.106	-.003	-.133	.111	-.050	.027	.034	-.087
Child/Adult Behavior Checklist									
Depressive Problems	.070	.140	.029	-.148	.037	.056	-.018	-.040	-.020
Anxious Problems	.018	.051	.020	-.093	.112	.161	.030	.036	.009
Withdrawn Problems	.055	.226	-.028	-.110	.083	-.063	.166	.074	.029
Somatic Complaints	.016	-.025	.044	-.162	.017	.133	.007	-.093	.021
Aggressive Behavior	.088	.127	-.088	-.261 [a]	-.119	.128	-.036	-.137	-.108
Rule-Breaking Behavior	-.008	-.004	-.096	-.192	-.027	.043	.156	-.035	-.008
Rosenberg Self-Esteem Scale	-.172	-.187	.081	.070	.049	.213	-.006	.086	-.109

Note. [a] <.05, [b] <.01, [c] <.001. Connections: 1=left temporal lobe-left putamen (DMN-RS), 2=left temporal lobe-left pallidum (DMN-RS), 3=right nucleus accumbens-left insula (RS-SN), 4 and 5=right nucleus accumbens-left ventral prefrontal cortex (RS-DMN), 6=right preC/PCC-left lateral prefrontal cortex (DMN-CEN), 7 and 8= left preC/PCC-right lateral ventral prefrontal cortex (DMN-CEN), 9=left intraparietal sulcus-right parietal medial cortex (CEN-SN). CEN=central executive network, DMN=default-mode network, SN=salience network, RS=reward system. ADOS-2=Autism Diagnostic Observation Schedule, Second Edition, CSS=Calibrated Severity Score.

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